20 Inconclusive diagnosis following newborn screening for cystic fibrosis (CF): clinical outcomes in 56 infants from three Spanish CF centres

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Objectives: To analyze sweat test and clinical outcomes of infants with Inconclusive diagnosis for CF identified through newborn screening (NS) from 2000 to 2012.
Methods: Retrospective cohort study using the CF Database of three CF Centers of Catalonia (Spain). Sweat values (ST), pancreatic status, clinical symptoms, pulmonary function and colonization with *Pseudomonas aeruginosa* or *Staphylococcus aureus* (SA) were analyzed.
Results: Inconclusive diagnoses for CF patients were identified. Most common mutations were: L997F (n = 13), 5T-12TG (n = 10), G576A-R668C-D443Y (n = 9), R117H-7T (n = 5), D1152H (n = 5), 5T-13TG (n = 4), and the remaining cases (n = 10) with individual CFTR mutations. The ST values were intermediate at newborn period in 25 cases. In three patients with F508del/5T-13TG and one with F508del/R117H-7H, CF diagnosis was reassigned after a positive ST and respiratory symptoms (developed 3–6 years later). All 50 cases have pancreatic sufficiency with normal BMI and normal lung function. SA was isolated occasionally in seven patients and PA in only one patient of the 25 cases.
Conclusion: Our results indicate that Inconclusive diagnosis for CF may be associated with the development of CF disease as previously reported in the literature. We found that the majority of infants with Inconclusive diagnosis remained well and free of signs of CF disease but careful monitoring and follow up of these patients are warranted.

21 Outcomes of children referred after positive cystic fibrosis (CF) newborn screening, who have a normal sweat test

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Objectives: CF newborn screening started in our region in 2007. The English protocol is based on IRT-DNA-IRT, and those suspected of having CF are referred for a sweat test. We assessed outcomes of those with a normal sweat chloride (<30 mmol/L) to ensure we had not missed a diagnosis.
Methods: A retrospective review of referral documentation and computer records, with subsequent telephone calls to the children's general practitioner.
Results: In 6 years, we were referred 181 children for sweat testing, 143 had a positive sweat test, and 34 children had a normal sweat test. 4 did not have the sweat test (all with lethal chromosomal abnormalities); 7 were diagnosed with CF based on 2 disease-causing mutations on the initial Guthrie test (that looks at 30 mutations); 2 were diagnosed later due to clinical suspicion (after extended genotyping). Of the remaining 25, 19 were confirmed to be healthy by the GP (6 months to 6 years later), 5 were lost to follow up, and the GP would not give details in 1 case. Comparing CF vs non-CF cases, there was no difference in mean IRT (165 vs 121 mmol/L) but mean sweat chloride was higher in the CF group (18.8 vs 10.1 mmol/L).
Conclusion: The diagnosis was based on 2 gene mutations in all cases, but 2 required extended genotyping – done due to clinical suspicion at the time of the sweat test. So far, no child has been re-referred with a late CF diagnosis.

22 IRT/IRT vs. IRT/PAP. Which is the best strategy? A pilot study

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Since 2002 a two-step IRT/IRT (immunoreactive trypsin) protocol has been used as a method of newborn screening for CF in every public maternity in Buenos Aires city. In order to optimize resources and reduce recitations, a prospective pilot study was conducted over a 6 months period.
Objective: To compare the IRT/IRT strategy with the IRT/Pancreatitis Associated Protein (PAP) method.
Methods: IRT and PAP determination were both performed in dry blood sample taken between 48–72 hours old. Infants with a raised first IRT measurement were recited for a second sample before 25 days of age. Delphia method was used to analyze IRT and Elisa for PAP. We considered a cut-off for abnormal IRT ⩾60 ng/ml and for PAP ⩾1.6 ng/ml with an IRT between 60–100 ng/ml and ⩾0.5 ng/ml with an IRT >100 ng/ml. Patients were referred for sweat test (ST) to confirm the diagnosis.
Results: There were 15,000 births from June to December 2011. From these, 105 patients (0.7%) had abnormal IRT and 83 children attended for the second sample (study population). Twenty children **(24%)** had the second IRT also abnormal and were referred to perform ST and molecular study. Only 6 children **(7.2%)** had abnormal PAP in the first sample and would be referred to ST. One patient had abnormal ST (IRT/IRT: 190/147 ng/ml; PAP: 1.95 ng/ml; homozygous p.F508del), 1 heterozygous carrier (G542X) presented an IRT/IRT positive, a normal PAP and a normal ST.
Conclusion: IRT/PAP strategy helps to reduce the recitation. Further studies will be necessary to address that the sensitivity and specificity of newborn screening has not been changed.

23 Implementation of a diagnostic work up after newborn screening for CF in Oslo, Norway

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Objectives: Newborn screening (NBS) for CF started on Mar 1st 2012. NBS positive infants are defined as
1. increased immunoreactive trypsinogen (IRT) and two CFTR mutations or
2. markedly elevated IRT levels.

Guidelines recommend that sweat testing (ST) is performed shortly after informing parents of a positive NBS. Long travel distances in Norway challenge this time factor.
Aim: To evaluate the diagnostic and logistics procedures after positive NBS at the Oslo CF centre.
Methods: A tight collaboration between the laboratory team, the CF team and the NBS program to assure diagnostic quality was organized. The number of NBS positive infants admitted from Mar 1st 2012 until Dec 31st 2013 was registered. Implementation of same day ST and fecal elastase (FE) measurements was recorded and the we evaluated the diagnostic work up performance.
Results: 22 NBS positive infants were followed up. Two newborns with meconium ileus were excluded. 20 infants thus had a diagnostic work up during one single day. The median time from birth until investigation was 33 days. A duplicate ST was performed by a specialist nurse, with a performance rate for a valid same day ST of 100%. FE was measured in all infants. Travel distances were up to 550 kilometers; however 19/20 had their scheduled appointment at the CF centre within two days after the telephonic information of a positive NBS. One infant with elevated IRT only was postponed due to summer vacation.
Conclusion: The diagnostic work up after a positive NBS for CF seems to be set up adequately at the Oslo CF centre. The performance rate of ST was excellent (100%), thus the CF physician could provide same day assessment of a CF diagnosis.